specification paragraph or the rewritten claims, the version presented in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections shall have precedence. Should any discrepancies be discovered in the rewritten abstract, the version presented on the separate sheet shall have precedence.

The amended abstract is fully supported by the application as filed, *inter alia*, the original abstract. The amended specification paragraph is fully supported by the application as filed, *inter alia*, at page 3, line 12 and ending at page 4, line 6. Amended claims 1-28 are fully supported by the application as filed, *inter alia*, original claims 1-28 respectively. Therefore, the amended abstract, amended specification paragraph, and amended claims 1-28 do not constitute new matter.

I. Information Disclosure Statement Objections

The Examiner has not considered a reference listed on Applicants Form PTO-1449 filed on November 15, 2001 because it contained a hyperlink. Applicants traverse this rejection and respectfully invite the Examiner's attention to MPEP §608.01 which states:

> If hyperlinks and/or other forms of browser-executable code are embedded in the text of the patent application, examiners should object to the specification and indicate to applicants that the embedded hyperlinks and/or other forms of browser-executable code are impermissible and require deletion. This requirement **does not apply to** electronic documents listed on forms PTO-892 and **PTO-1449** where the electronic document is identified by reference to a URL. MPEP §608.01, second paragraph under the heading" Hyperlinks and Other Forms of Browser-Executable Code in the Specification" (emphasis added).

Therefore, Applicants believe that listing a hyperlink on PTO-1449 is permissible. Applicants enclose herewith a new Form PTO-1449 listing this reference. Applicants have added to the PTO-1449 the title of the document posted at this hyperlink and the date the data (GenBank Release 128.0) was released according to the web site. Applicants also provide a printed copy of a portion of the contents of this web page.

II. Abstract Objections

The Examiner has objected to the form of the abstract of the instant application as having more than one paragraph. In response, Applicants have amended the Abstract. Applicants believe that the amended Abstract complies with MPEP §608.01(b) and, therefore, respectfully request withdrawal of this rejection.

III. Claim Objections

The Examiner has objected to claims 1-28 for failing to begin with an article. The Examiner has objected claims 20 and 21 for reciting "ID NO" rather than "SEQ ID NO". The Examiner has further objected to claim 21 as referring to SEQ ID NO:13 as a cytochrome P-450 when it is a reverse primer. In response, Applicants have amended claims 1-28 according to the Examiner's suggestions. Therefore, Applicants, respectfully request withdrawal of these objections.

IV. Rejections Under 35 U.S.C. § 101

Claims 1-8 and 12-23 have been rejected under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter, namely products of nature. The Examiner has suggested amending the claims to recite "An isolated DNA sequence...." Consistent with this suggestion, Applicants have amended claims 1-8 and 12-23 to recite "A recombinant non-yeast DNA...." and, therefore, respectfully request withdrawal of this rejection.

V. Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-28 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that the Applicant regards as the invention.

The Examiner alleges that claims 1-28 are unclear as to what sequences are being claimed, sequences comprising codons poorly suited to expression in yeast or sequences comprising replaced codons. In response, Applicants have amended claims to indicate that they are drawn to recombinant non-yeast DNA molecules having replaced codons.

The Examiner further alleges that claims 1-28 are unclear as to what constitutes a "sufficient number" of codons and as to the boundary between "poorly suited to yeasts" and "well suited to yeasts." In response, Applicants respectfully wish to invite the Examiner's attention to the definition of "sufficient number" provided in the disclosure at page 5, lines 4-15. The specification clearly indicates that

> within the meaning of the present invention, 'sufficient number of codons' is understood as being the number of codsons which it is necessary and sufficient to replace in order to observe a substantial improvement in their exprssion in yeasts

Page 5, lines 4-8. The specification further indicates preferred percentages of replacement. Page 5, lines 9-15. Applicants assert that, in view of this definition and the general knowledge of the skilled artisan, claims 1-28 are clear and definite. *See e.g. Markman v. Westview Instruments*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd* 517 U.S. 317 (1996)("For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims.").

The Examiner also alleges that claims 1-8 and 12-28 are unclear as to the meaning of the phrase "corresponding codons." In response, Applicants wish to respectfully invite the Examiner's attention to the definition of "corresponding codons" provided in the disclosure at page 4, lines 7-14. The specification teaches what is well understood in the art as what is meant by a corresponding codon, i.e. that an amino acid may be encoded by more than one codon – these codons are corresponding codons. Applicants assert that, in view of these definitions and what is known in the art, amended claims 1-8 and 12-28 are clear and definite. *See e.g. Markman*, 52 F.3d at 980.

The Examiner also alleges that claims 9-11 are unclear as to what constitutes a "high content of leucine" codons. Applicants respectfully invite the Examiner's attention to the

definition of "high content of leucine" provided in the disclosure at page 6, lines 10-16, which generally teaches what is known in the art as a high content of leucine codons. Applicants assert that, in view of these definitions and the knowledge of the skilled artisan, amended claims 9-11 are clear and definite. *See e.g. Markman*, 52 F.3d at 980.

The Examiner alleges that claims 13-19, 21, and 25-27 are unclear as to the antecedent basis for "it" in the phrase "characterized in that it." Applicants have amended 13-19, 21, and 25-27 claims such that they do not cite ranges of varying scope or recite the phrase "characterized in that it."

Lastly, the Examiner alleges that claims 2-8 and 12-28 are unclear for reciting ranges of varying scope. Applicants wish to respectfully invite the Examiner's attention to the definition of "poorly suited to yeasts" provided in the specification at page 3, lines 12-18. The specification enumerates several specific codons which have been described in the art and which are considered "poorly suited to yeasts." Applicants also wish to invite the Examiner's attention to the definition of "well suited to yeasts" provided in the specification at page 4, lines 7-14. Here, the specification enumerates several specific codons which are considered "well suited to yeasts." That it is known in the art that there are codons that are well suited and poorly suited in organisms is further highlighted by Hoekema et al., 1987, Molecular and Cellualr Biology 7:2914-2924, cited by the Examiner in his 35 U.S.C. § 102(b) rejections further addressed below. Applicants assert that, in view of these definitions and the knowledge of the skilled artisan, claims 2-8 and 12-28 are clear and definite with respect to the boundary between poorly suited and well suited codons. *See e.g. Markman*, 52 F.3d at 980.

Since all amended claims are clear and definite in view of the disclosure, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. §112, second paragraph.

VI. Rejections Under 35 U.S.C. § 102(b)

Claims 1-8, 12, 13, 18, and 22-26 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Hoekema et al., 1987, Molecular and Cellular Biology 7:2914-2924 (herein after "Hoekema"). The Examiner alleges that Hoekema discloses genetic manipulation of phosphoglycerate kinase (PKG1) comprising codon replacement.

Applicants traverse this rejection and assert that the instant claimed invention is not anticipated by Hoekema. For a document to anticipate, it must teach each and every element of the claims. *See e.g.* MPEP §2131.

Hoekema appears to disclose that codon replacement of major or preferred codons in a gene by minor or non-preferred codons results in lower levels of gene expression. *See e.g.* Hoekema, Abstract. Hoekema does not teach the opposite, *i.e.* replacing minor codons with major ones, which is the subject matter of the claims of the present Application. In addition, the codon replacement apparently taught by Hoekema is limited to a single **yeast** gene as noted by the Examiner in his rejection under 35 U.S.C. § 103(a). *See* Hoekema, p. 2915, right column, second full paragraph. The instant claims, however, recite "recombinant *non-yeast* DNA" (emphasis added). Since Hoekema fails to teach each and every element of claims 1-8, 12, 13, 18 and 22-26, as amended. Applicants respectfully request that the rejection of claims 1-8, 12, 13, 18 and 22-26 under 35 U.S.C. § 102(b) be withdrawn.

VII. Rejections Under 35 U.S.C. § 103(a)

Claims 15-17 and 27 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hoekema in view of Neill et al., 1987, Gene 55:303-317 (herein after "Neill"). The Examiner states that Hoekema does not teach sequences from plants nor does Hoekema teach a process for producing a heterologous protein in a transformed yeast cell. The Examiner alleges that Neill teaches a method for expressing wheat α-gliadin in *Saccharomyces cerevisiae*. The Examiner alleges the artisan of ordinary skill would have been motivated to optimize the expression of the plant gene of Neill according to the codon replacement method of Hoekema.

Applicants traverse this rejection and assert that Hoekema and Neill, whether considered separately or in combination, fail to teach each and every element of the claims. As noted in the preceding section, Hoekema actually teaches replacement of major yeast codons with minor codons, where as claims 15-17 and 27 are directed to a recombinant non-yeast DNA which has minor codons (poorly suited in yeast) with major codons (well suited in yeast), wherein said DNA is expressed in yeast. Thus, it is inconceivable that a person of ordinary skill in the art would be motivated by Hoekema to obtain a plant gene expressible in yeast by replacing major yeast codons with minor codons. Any other combination of Hoekema and Neill would impermissibly require modification of Hoekema's principle of operation. *See* MPEP §2143.01, p. 2100-125. In addition, Neill actually teaches away from the present invention because, Neill teaches that the most critical factors affecting gene expression levels were unknown. *See* Neill, p. 313, last paragraph *et seq.* ([O]bservations of lower than expected levels of protein production have been made in other (but not all) yeast expression studies.... At present, this phenomenon is not fully understood, though altered transcription or translation rates, protein or mRNA instability, protein toxicity and codon usage biases have been suggested as factors.). Therefore, the asserted combination of references would have required the artisan of

ordinary skill to proceed without an expectation of success. *See* MPEP §2143.02. Since Hoekema and Neill, whether considered separately or in combination, fail to teach or suggest every element of the claimed invention, Applicants respectfully request withdrawal of this rejection.

VIII Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance.

Applicants have enclosed the fee for a two-month extension of time as required under 37 C.F.R. §1.17(a)(1). Applicants do not believe any additional fee is required for this filing. Nevertheless, the Commissioner is hereby authorized to charge any fees required for this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Two copies of this page are enclosed.

Respectfully submitted,

August 15, 2002

Louis S. Sorell
PTO Reg. No. 32,439

Alicia A. Russo
PTO Reg. No. 46,192

BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2620

Attorneys for Applicants

Enclosures

VERSION WITH MARKINGS TO SHOW CHANGES MADE

This marked-up version was prepared with DeltaView software (v2.5.163). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

IN THE SPECIFICATION

The abstract has been amended as follows:

The present invention relates to a ~~DNA sequence~~recombinant non-yeast DNA, which encodes a protein of interest ~~which~~, wherein an unmodified DNA corresponding to the recombinant non-yeast DNA contains ~~regions~~a region having a high content of codons ~~which~~that are poorly suited to yeasts, ~~characterized in that a sufficient~~wherein a number of the codons ~~which~~that are poorly suited to yeasts ~~is~~are replaced in said region of the recombinant non-yeast DNA with ~~corresponding~~synonymous codons ~~which~~coding for the same amino acid that are well-suited to yeasts, ~~in~~ and wherein the ~~said regions having a high content~~number of replaced codons ~~which are poorly suited~~is sufficient to permit expression in yeasts. The present invention also relates, ~~more specifically~~, to DNA sequences which originate from dicotyledonous or monocotyledonous plants, in particular plants of the graminae family which are selected~~, in particular,~~ from among wheat, barley, oats, rice, maize, sorghum and cane sugar~~. The present invention also relates~~ ,as well as to vectors and transformed yeasts which contain ~~a~~ the DNA sequences aaccording to the invention.

The paragraph beginning at page 3, line 12 and ending at page 4, line 6 has been amended as follows:

Within the meaning of the present invention, "codons which are poorly suited to yeasts" are understood as being codons whose frequency of use by yeasts is less than or equal to approximately 13 per 1000, preferably less than or equal to approximately 12 per 1000, more preferably less than or equal to approximately 10 per 1000. The frequency at which codons are used by yeasts, more specifically by *S. cerevisiae*, is described, in particular, in "Codon usage ~~data base from~~database" by Yasukazu Nakamura" (~~http://www.dna.affrc.go.jp/~nakamura/codon.html~~available on the Kazusa world wide web server). This applies, in particular, to codons CTC, CTG and CTT, which encode leucine, to codons CGG, CGC, CGA, CGT and AGG, which encode arginine, to codons GCG and GCC, which encode alanine, to codons GGG, GGC and GGA, which encode glycine, and to codons CCG and CCC, which encode proline. The codons which are poorly suited to yeasts in accordance with the invention are, more specifically, codons CTC and CTG, which encode leucine, CGG, CGC, CGA, CGT and AGG, which encode arginine, codons GCG and GCC, which encode alanine, GGG and GGC, which encode glycine, and codons CCG and CCC, which encode proline.

IN THE CLAIMS

Claims 1-28 have been amended as follows:

1. (AMENDED) ~~DNA sequence~~A recombinant non-yeast DNA, which encodes a protein of interest ~~which~~, wherein an unmodified DNA corresponding to the recombinant non-yeast DNA contains ~~regions~~a region having a high content of codons ~~which~~that are poorly suited to yeasts, ~~characterized in that a sufficient~~wherein

a number of the codons ~~which~~that are poorly suited to yeasts ~~is~~are replaced in said region of the recombinant non-yeast DNA with ~~corresponding~~synonymous codons ~~which~~coding for the same amino acid that are well-suited to yeasts, ~~in~~wherein the ~~said regions having a high content~~number of replaced codons ~~which are poorly suited~~is sufficient to permit expression in yeasts.

2. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 1, ~~characterized in that~~wherein the ~~codons which are~~ poorly suited ~~to yeasts~~codons are selected from ~~among~~the group consisting of codons whose frequency of use by yeasts is less than ~~or equal to approximately~~about 13 per ~~1000, preferably less than or equal to approximately 12 per 1000, more preferably less than or equal to approximately 10 per 1000.~~1000 codons.

3. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 2, ~~characterized in that~~ wherein the ~~codons which are~~ poorly suited ~~to yeasts~~codons are selected from ~~among codons~~the group consisting of CTC, CTG and CTT, which encode leucine, ~~codons~~ CGG, CGC, CGA, CGT and AGG, which encode arginine, ~~codons~~ GCG and GCC, which encode alanine, ~~codons~~ GGG, GGC and GGA, which encode glycine, and ~~codons~~ CCG and CCC, which encode proline.

4. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 3, ~~characterized in that~~ wherein the ~~codons which are~~ poorly suited ~~to yeasts~~codons are selected from ~~among codons~~the group consisting of CTC and CTG, which encode leucine, ~~codons~~ CGG, CGC, CGA, CGT and AGG, which encode arginine, ~~codons~~

GCG and GCC, which encode alanine, ~~codons~~ GGG and GGC, which encode glycine, and ~~codons~~ CCG and CCC, which encode proline.

5. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one of claims 1 to 4, characterized in~~claim 1, wherein the codons that ~~the corresponding codons which~~ are well- suited to yeasts are selected from ~~among~~the group consisting of codons ~~which correspond to the codons which are poorly suited to yeasts and which encode the same amino acids, and~~ whose frequency of use by yeasts is greater than 15 per ~~1000, preferably greater than or equal to 18 per 1000, more preferably greater than or equal to 20 per 1000.~~ 1000 codons.

6. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 5, ~~characterized in that~~wherein the ~~corresponding codons which are~~ well- suited ~~to yeasts~~codons are selected from ~~among codons~~the group consisting of TTG and TTA, ~~preferably TTG,~~ which encode leucine, ~~codon~~ AGA, which encodes arginine, ~~codons~~ GCT and GCA, preferably GCT, which encode alanine, ~~codon~~ GGT, which encodes glycine, and ~~codon~~ CCA, which encodes proline.

7. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one of claims 1 to 7, characterized in that~~claim 1, wherein the ~~regions~~region having a high content of codons ~~which~~that are poorly suited to yeasts ~~contain~~contains at least 2 poorly suited codons among 10 consecutive codons, ~~with it being possible for~~wherein the ~~two~~poorly suited codons ~~to be~~are adjacent or ~~separated by up~~nonadjacent to ~~8~~each other ~~codons~~.

8. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 7, ~~characterized in that~~wherein the ~~regions~~region having a high content of poorly suited codons ~~contain~~contains 2, 3, 4, 5 or 6 poorly suited codons per 10 consecutive codons, or contain at least 2 or 3 adjacent poorly suited codons.

9. (AMENDED) ~~DNA, in particular cDNA, sequence~~A recombinant non-yeast cDNA, which encodes a protein of interest ~~which~~, wherein an unmodified DNA corresponding to said recombinant non-yeast DNA contains ~~regions having a high content of leucine, characterized in that a sufficient number of CTC codons encoding leucine in the said~~ region ~~having a~~of high ~~content of leucine is replaced with TTG and/or TTA codons, or in that a sufficient number of~~ CTC ~~and~~ codon or high CTC+CTG ~~codons encoding leucine in the said region having a high~~codon content, wherein a number of ~~leucine is~~said CTC codons and/or CTG codons are replaced in said recombinant non-yeast DNA with TTG and/or TTA codons, and wherein the number of replaced codons is sufficient to permit expression in yeasts.

10. (AMENDED) ~~Sequence~~The recombinant non-yeast cDNA according to claim 9, ~~characterized in that~~wherein the CTC ~~or CTC~~codon(s) and/or the CTG ~~codons~~codon(s) are replaced with ~~a~~ TTG codon(s).

11. (AMENDED) ~~Sequence~~The recombinant non-yeast cDNA according to ~~one of claims 9 or 10, characterized in that~~claim 9, wherein the ~~regions~~region having a high content of leucine ~~contain~~contains 2, 3, 4, 5 or 6 leucines per 10 consecutive amino acids, or contain at least 2 or 3 adjacent leucines.

12. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one of claims 1 to 11, characterized in that~~claim 1, wherein the general content of poorly suited codons in the corresponding unmodified DNA is at least 20%~~, more preferably at least 30%, as compared with~~ of the total number of codons.

13. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one of claims 1 to 12, characterized~~claim 1, wherein replaced codons are in ~~that it contains at least one~~the 5' region ~~having a high content of codons which are poorly suited to yeasts~~.

14. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 13, ~~characterized in that the codons which are poorly suited to yeasts are~~wherein replaced codons are only in ~~this~~the 5' region.

15. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one of claims 1 to 14, characterized in that it~~claim 1, wherein the corresponding unmodified DNA is ~~an isolated DNA sequence of natural origin, in particular of~~a plant ~~origin~~DNA.

16. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 15, ~~characterized in that it originates~~wherein the corresponding unmodified DNA is selected from the group consisting of a dicotyledonous ~~or~~plant DNA and a monocotyledonous ~~plants, in particular from monocotyledonous plants~~plant DNA.

17. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 16, ~~characterized in that it originates from plants of~~wherein the ~~graminae family, which are~~corresponding unmodified DNA is selected~~, in particular,~~ from ~~among~~the group

consisting of a wheat DNA, a barley DNA, ~~oats~~an oat DNA, a rice DNA, a maize DNA, a sorghum DNA, and a cane sugar DNA.

18. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to ~~one~~claim 1, wherein the protein of ~~claims 1 to 17, characterized in that it encodes~~interest is an enzyme.

19. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 18, ~~characterized in that it encodes~~wherein the enzyme is a cytochrome P450.

20. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim 19, ~~characterized in that~~wherein the corresponding unmodified DNA has a nucleotide sequence ~~which contains regions having a high content~~selected from the group consisting of ~~codons which are poorly suited to yeasts includes the coding region of the sequences~~SEQ ID ~~No.~~ NO:1 ~~or~~and SEQ ID ~~No.~~ NO:10.

21. (AMENDED) ~~Sequence~~The recombinant non-yeast DNA according to claim ~~19,~~ ~~characterized in that it is one of~~19 having a nucleotide sequence selected from the ~~sequences~~group consisting of SEQ ID ~~No.~~ NO:7, SEQ ID ~~No.~~ NO:8, SEQ ID ~~No. 9~~NO:9, and SEQ ID ~~No. 13.~~NO:14.

22. (AMENDED) ~~Chimeric~~A chimeric gene which ~~contains~~comprises a ~~modified~~recombinant non-yeast DNA sequence according to ~~one of claims~~claim 1 operably linked to ~~21 and~~ heterologous 5' and 3' regulatory elements which are able to function in a yeast.

23. (AMENDED) ~~Vector for transforming yeasts which contains~~A yeast transformation vector comprising at least one chimeric gene according to claim 22.

24. (AMENDED) ~~Process~~A process for transforming ~~yeasts~~a yeast cell using a vector according to claim ~~23.~~23 comprising contacting a yeast cell with said vector under conditions that permit said yeast cell to take up said vector.

25. (AMENDED) ~~Transformed~~A transformed yeast for expressing a protein of interest, ~~characterized in that it contains a~~comprising the chimeric gene according to claim 22.

26. (AMENDED) ~~Yeast~~The yeast according to claim 25, ~~characterized in that~~wherein it is selected from ~~among~~ the ~~genera~~group consisting of *Saccharomyces, Kluyveromyces, Hansenula, Pichia* and *Yarrowia*~~, advantageously from the genus *Saccharomyces*, in particular *S. cerevisiae*~~.

27. (AMENDED) ~~Process~~A process for producing a heterologous protein of interest in a transformed yeast, ~~characterized in that it comprises the steps of~~comprising:

a) transforming a yeast with a vector ~~according to claim 23~~ which contains a ~~modified~~recombinant non-yeast DNA ~~sequence~~ according to ~~one of claims~~claim 1 operably linked to ~~21 and~~ heterologous 5' and 3' regulatory elements which are able to function in a yeast~~;~~;

b) culturing the transformed yeast~~;~~; and

c) extracting the protein of interest from the yeast culture.

28. (AMENDED) ~~Process~~A process for transforming a substrate by enzymic catalysis using an enzyme which is expressed in a yeast~~, which process comprises the steps of~~ comprising:

a) culturing, in the presence of the substrate to be transformed, the yeast ~~which has been transformed with a vector~~ according to claim ~~23 which contains a modified DNA sequence according to one of claims 1 to 21~~25; and ~~heterologous 5' and 3' regulatory elements which are able to function in a yeast, and then~~

b) recovering the transformed substrate from the yeast culture.